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# Nutrition and Renal Disease I

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# BORDEN'S REVIEW
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# Nutrition and Renal Disease I

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## GLOSSARY

1. *ADH* — Antidiuretic hormone secreted by the posterior pituitary gland; it acts on the kidney to cause an increase in the reabsorption of water, causing a concentrated urine to be formed.
2. *Albuminuria* — The presence of abnormally large amounts of albumin in the urine.
3. *Anorexia* — Poor appetite.
4. *Azotemia* — Abnormal elevation of urea nitrogen in blood.
5. *Diuresis* — Increase in urine volume.
6. *GFR* — Rate of glomerular filtration; the amount of fluid filtered by the glomeruli from the plasma in unit time.
7. *Glycosuria* — Abnormally large amount of sugar (glucose) in urine.
8. *Hematuria* — Presence of blood in the urine.
9. *Hyper-* or *hypochloremia* — Respectively, increase or decrease in the concentration of chloride in the serum from the normal range of 100-105 mEq./L.
10. *Hyper-* or *hypokalemia* — Respectively, increase or decrease in the concentration of potassium in the serum from the normal range of 4-5 mEq./L.
11. *Hyperlipemia* — Excessive fat or lipid in the serum.
12. *Hyper-* or *hyponatremia* — Respectively, increase or decrease in the concentration of sodium in the serum from the normal range of 135-140 mEq./L.
13. *Hyperplasia* — Abnormal increase in the number of normal cells in a tissue.
14. *NPN* — Non-protein nitrogen; includes urea, creatinine, uric acid and amino acids.
15. *Oliguria* — Small urine volume.
16. *Polyuria* — Large urine volume.
17. *Proteinuria* — Presence of abnormally large amounts of protein in urine.

## INTRODUCTION

This review will discuss the nutritional aspects of some of the frequently encountered diseases of the kidney. In order to avoid a repetitious discussion of separate disease entities, the author has sought to present the basic metabolic patterns common to a number of diseases. The following classifications will be followed: In Part I, (a) acute glomerulonephritis, (b) chronic renal failure. In Part II, (c) acute renal failure, (d) the nephrotic syndrome, (e) disorders of the renal tubule and (f) potassium deficiency nephropathy. Because rational dietary therapy can be formulated only in terms of a thorough understanding of the basic physiological abnormalities, emphasis will be placed upon understanding these abnormalities. The therapeutic implications will be drawn accordingly. Strictly clinical and pathological aspects of the diseases will be briefly discussed for purposes of orientation. Authoritative discussions of these points are available in standard works (1-4) to which the interested reader is referred.

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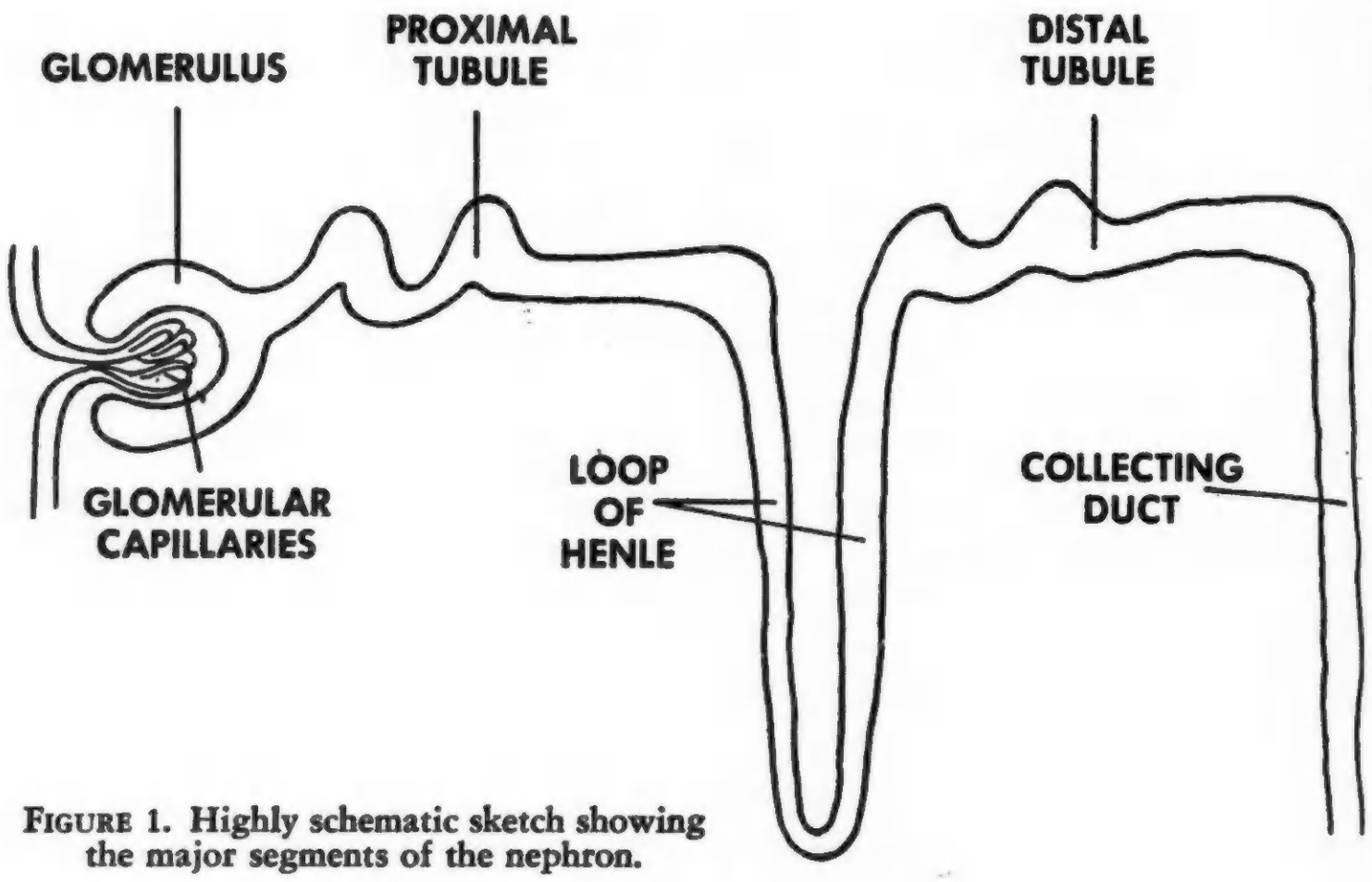


FIGURE 1. Highly schematic sketch showing the major segments of the nephron.

## PHYSIOLOGICAL CONSIDERATIONS (5)

The functional unit of the kidney is the nephron, (Fig. 1) of which there are approximately one million in each kidney. Each nephron consists successively of a glomerulus, proximal tubule, loop of Henle, distal tubule and collecting duct. At the glomerulus, a portion of the blood flowing through the capillary loops undergoes filtration, forming glomerular filtrate, a fluid nearly identical to the plasma except for its low content of protein. The rate of glomerular filtration is astoundingly large, being nearly 180 liters per day in a healthy individual. Considering that the average urine volume is only one to two liters per day, it is obvious that much of the glomerular filtrate is reabsorbed during its transit along the tubules. This reabsorption is not merely a bulk return of filtrate to the plasma; rather, many changes in composition occur as the result of tubular activity. In fact, the final bladder urine is so radically different from the filtrate, both in volume and in composition, that the nature of this precursor fluid (*i.e.*, the glomerular filtrate) could hardly be surmised.

*Proximal Tubular Functions:* In the proximal tubule, approximately 80 to 85% of the water and solutes of the filtrate undergo reabsorption. This reabsorption is selective to the exent that all of the glucose and most of the phosphate, sulfate and amino acids are removed, as well as a large portion of the filtered sodium, chloride, bicarbonate and urea. The processes responsible for the removal of many of these substances require metabolic energy, and hence they are referred to as "active processes." Water reabsorption, on the other hand, is thought to be an osmotic consequence of the reabsorption of solutes and hence is "passive." As a result of the latter, the concentration of the urine at the end of the

proximal tubule is the same as the plasma (isotonic*) even though the composition of the urine has been considerably altered.

*Concentration and Dilution Mechanisms* (6): During the passage of the tubular urine through the loop of Henle, further alterations occur. The nature of these is not completely known. Since the urine issuing from the loop of Henle is quite hypotonic with respect to plasma, it is apparent that there has been a movement of solute (probably sodium and chloride) outward from the tubular urine into the interstitial space of the renal papillae through which these loops descend and reascend to the cortex to connect with the distal tubule. This transport of solute from the loops is related to the concentrating process and implies that the medullary interstitial fluid must be hypertonic to the plasma.

Under circumstances where a concentrated urine is to be formed, antidiuretic hormone (ADH) is secreted by the posterior pituitary gland; ADH acts upon the cells of the distal tubule to allow water reabsorption in excess of solute in this segment of the nephron. Hence, the urine entering the distal tubule is hypotonic, but as it leaves the distal tubule, it is again isotonic and considerably reduced in volume. The final concentrating process resides in the collecting ducts which anatomically traverse the hypertonic interstitial region of the medulla as they empty into the larger collecting systems and eventually into the renal pelvis. As the isotonic tubular urine passes through this hypertonic environment, water is drawn from the tubule into the interstitial space, reducing the volume of urine and increasing its concentration to hypertonic levels.

Somewhat in contrast to the above is the sequence of events when a dilute urine is formed. Under these circumstances ADH secretion is reduced, and there is relatively little water reabsorption by the distal tubule. Hence, a large volume of hypotonic urine leaves the distal tubule and enters the collecting duct. As it passes through the hypertonic medulla, it may lose some water, but the volume is so large relative to the amount of water being reabsorbed that the final urine is still of large volume and quite dilute.

The contrast between the diluting and the concentrating mechanisms emphasizes the role of ADH in the economy of body water. There is appreciable experimental evidence concerning the factors controlling rate of secretion of this hormone by the posterior pituitary gland. Of prime importance is the effective osmostic pressure of the body fluids, which under nearly all circumstances is reflected by parallel changes in the concentration of sodium in the serum. Under conditions of hypernatremia, *e.g.*, pure water deficit, ADH secretion

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*Throughout this discussion, the term isotonic and hypo- and hypertonic will be used frequently. These terms refer to the osmotic pressure, isotonic meaning having the same osmotic pressure as plasma, hypo- and hypertonic indicating less than or greater than plasma .The terms iso-osmotic, hypo- or hyperosmotic may be used interchangeably with iso-, hypo- or hypertonic. Osmotic pressure varies with total number of particles of a solution (total solutes) and is independent of the nature of the particles. The normal plasma has an osmotic pressure of about 280 mOs/L. Specific gravity bears only an approximate relation to osmotic pressure; a specific gravity of 1.010 corresponds approximately to isotonicity.

is increased and a concentrated urine is formed. On the other hand, ingestion of excess water dilutes the body fluids and reduces the serum sodium thereby reducing the ADH secretion, and a copious dilute urine is formed.

The magnitude of the adjustments which the ADH-renal mechanism can perform in the interest of conserving or excreting water may be inferred from the fact that the normal kidney can on the one hand concentrate the urine to about 4 times the plasma concentration (1200 mOs/L) and on the other hand can dilute the urine to 40 mOs/L. Urine volume may be varied from about 0.4 ml/min with antidiuresis to 15 ml/min with brisk water diuresis.

The rate of solute excretion exerts an important influence upon the concentrating ability of the kidney (7) and deserves some discussion in view of its applicability to some of the disturbed physiology encountered in chronic renal failure. Even in the presence of maximal ADH a fairly dilute (though still hypertonic) urine of large volume may be formed. This occurs because there is a reduction in reabsorption of solute and water by the proximal tubule. If, instead of the usual 85% of the filtered solute and water being reabsorbed, there were only 70% reabsorbed, then the amount of fluid reaching the loop of Henle would be doubled. Such a large volume of isotonic fluid apparently "overwhelms" even the maximal operation of the concentrating mechanism and results in the formation of a fairly dilute urine of large volume. Theoretically there are two possible mechanisms whereby this could occur: (a) some intrinsic limitation upon active sodium and chloride reabsorption or (b) the presence of large amounts of poorly reabsorbed or non-reabsorbable solutes (*e.g.*, urea, mannitol, glucose) in the tubular urine, restricting the passive diffusion of water and probably the active reabsorption of other solutes. Not only is there polyuria under these circumstances, there is also an appreciable loss of sodium in the urine apparently because of the delivery of this ion to the distal sites in amounts exceeding their maximal capacity for reabsorption.

*Acidification Mechanisms* (8): It is well known that the pH of the body fluids is delicately regulated, with extremes beyond pH 7.0 to 8.0 being incompatible with life. Although the buffer systems of the body fluids play an important immediate role in maintaining this narrow pH adjustment, it is ultimately the kidneys that are called upon to correct the disturbance permanently. This adjustment is believed to be primarily a function of the distal tubule. Of principal interest to this discussion is the mechanism whereby the kidney corrects the abnormalities incident to the introduction of strong acids into the body fluids. The net effect of this renal adjustment is a loss of hydrogen ions in the urine. Obviously, hydrogen ions do not exist free in the urine to any appreciable extent; rather, these hydrogen ions appear "bound" in two forms: titratable acid and ammonium ion. The source of these hydrogen ions is carbon dioxide which within the renal tubular cells is hydrated under the influence of the enzyme carbonic anhydrase to form carbonic acid. Carbonic acid is then the source of hydrogen ions which appear in the urine. Under conditions where an acid urine

is to be formed, sodium ions in the tubular urine are believed to be reabsorbed in exchange for hydrogen ions, which are excreted by the cells into the tubular urine. The hydrogen ions may then undergo any of the following three reactions:

(a) $HCO^-_3 + H^+ \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$ (diffuses back to plasma)

(b) $HPO^=_4 + H^+ \rightarrow H_2PO^-_4$ (titratable acid)

(c) $NH_3$ (from renal cells) $+ H^+ \rightarrow NH^+_4$ (ammonium ion in urine)

Reaction (a) accounts for the reabsorption of bicarbonate. Reactions (b) and (c) account for the accelerated excretion of titratable acid and ammonium ion in the urine. Note also that since carbonic acid is the source of the hydrogen ions, for each mole of $H^+$ secreted into the urine, one mole of bicarbonate is returned to the plasma. It is as if the kidney is infusing the plasma with bicarbonate as it secretes hydrogen ions into the urine.

*Excretion of Potassium:* Potassium is filtered at the glomerulus and is believed to undergo virtually complete reabsorption in the proximal tubule (9). The potassium which appears in the urine is thought to be the result of tubular secretion. The mechanism of secretion of this ion is intimately linked to the acidification mechanism. In this view, intracellular potassiums conceived as "competing" with intracellular hydrogen (derived from carbonic acid, see above) for secretion in exchange for sodium ion reabsorption (8). Conditions favoring acidification of the urine favor $H^+$ secretion. However, in conditions of alkalosis, $K^+$ excretion is favored. With the development of body potassium depletion, the intracellular potassium level of the tubular cells presumably falls, $H^+$ secretion is therefore increased and the urine then becomes acid.

*Urea Excretion* (5): Urea is the major end product of protein metabolism and is one the chief constituents of the urine. Urea is completely filterable at the glomerulus and undergoes a variable degree of reabsorption by the tubules. In contrast to the "active" character of the reabsorptive processes involved with many of the substances already discussed, the reabsorption of urea is a passive process involving back-diffusion from tubular lumen into plasma. The amounts of urea back-diffusing from the tubular urine are markedly dependent upon the urine flow, being large when there is oliguria and smaller when urine flow is large. Although tubular reabsorption is variable, it should be recognized that the rate of excretion of urea is markedly dependent upon the rate of glomerular filtration. This important point will be alluded to again in the discussions below.

*Phosphate Excretion:* Inorganic phosphate of the plasma is filtered at the glomerulus and undergoes reabsorption in the proximal tubule. Like other active reabsorptive processes, the maximal rate at which phosphate can be reabsorbed is limited; if the amount of phosphate being filtered exceeds this maximum, the remainder is excreted in the urine. One of the important influences upon the

maximal rate of phosphate reabsorption is the parathyroid hormone, secretion of parathyroid hormone being associated with marked falls in the maximal reabsorption of phosphate (10).

## ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis is one of the more common renal diseases of childhood. Most often the disease develops after a streptococcal infection, and it is believed to be the result of an immunologic response to certain nephritogenic strains of streptococci.

The clinical picture shows great variability, from a subclinical case on the one hand to a severe, even fatal, case on the other. The classical findings are edema of the eyelids associated with a scant urine volume. The urine has a dark coloration ("smoky urine") due to the presence of partly decomposed red blood cells. Slight generalized edema is common, but marked edema is rare. Hypertension to some degree occurs in most cases and is thought to be due to vasospasm. Severe or abrupt changes in blood pressure may be accompanied by a picture of hypertensive encephalopathy characterized by convulsions, drowsiness, and visual disturbances.

The course of acute glomerulonephritis is variable. Generally, the acute phase lasts from several days to a week and is terminated by a diuresis. Following this phase there is often a prompt return of well-being; renal function, however, returns more slowly, and red blood cells and casts may persist in the urine for some weeks or months. Complete recovery is the rule, although a small number of cases may progress to chronic renal disease and eventual renal failure.

### *Pathophysiology*

The principal functional abnormality in acute glomerulonephritis is a reduction in the rate of glomerular filtration (GFR) presumably due to the proliferative lesion of the glomeruli observed histologically (5). The oliguria so characteristic of the disease in the early stages is not only due to a reduction in GFR but also to the avid reabsorption of sodium and water by the proximal tubule, which occurs when GFR is reduced. The cause of the edema of acute glomerulonephritis may have its origin in this abnormality of tubular function, although the matter is still disputed.

One of the consequences of the reduction of GFR is the increase in blood urea. It is important to realize that the absolute level of urea in the serum under any conditions is dependent not only upon the rate of glomerular filtration and urine flow but also on the existing level of urea production from the metabolism of protein. The latter, in turn, is dependent upon the level of protein ingested or upon the amount of endogenous protein being catabolized. These considerations have very significant practical implications in the interpretations of blood urea values.

Reduction of GFR is also responsible for retention of phosphate and sulfate derived from the metabolism of protein. Being acidic substances, they tend to produce a metabolic acidosis, although this is rarely severe in acute glomerulonephritis. Potassium retention as manifested by a slight elevation of serum occurs to some extent during the oliguric phase of the disease. Serious degrees of hyperkalemia endangering cardiac function are not common, although they may occur with surprising rapidity and for reasons that are not entirely clear. The possibility of this serious complication should always be borne in mind.

### *Nutritional Considerations*

The diet prescribed for patients with acute glomerulonephritis must allow for the functional abnormalities exhibited by these patients as revealed in the clinical and chemical data.

In general during the acute phase of the disease, appetite is poor and vomiting may occur frequently. For these reasons, it is unrealistic to attempt to provide a diet adequate in all respects. For the same reason, the controversy concerning optimal protein intake of such patients is largely academic, since the diet consumed by the patients is nearly always low in protein simply because of anorexia.

As a minimum, one should concentrate upon adequacy of fluid intake and upon the provision of non-protein calories. With respect to water requirements, these should approximate the urine volume plus an additional increment for the insensible loss. Attempts to "open up the kidneys" by forcing fluids orally or parenterally are ill-advised, since they are ineffective and can only increase edema and may produce hyponatremia. Some degree of salt restriction is desirable in the presence of generalized edema or hypertension, although if possible a completely salt-free regimen should be avoided since it will diminish an already poor appetite. With respect to caloric intake, a minimum aim should be to provide about ¼ of the estimated total caloric expenditure as carbohydrate. This amount will prevent starvation ketosis and will retard endogenous protein catabolism (11). To be effective, the carbohydrate must be evenly distributed throughout the day and night rather than being given all at one time during the day.

To achieve these simple aims, the most satisfactory approach is to offer sweetened juices, tea or ginger ale. Total fluid intake and daily urine volume must be measured; any significant deficits of water should be treated by a slow parenteral infusion of glucose or invert sugar. In the presence of or threat of serious potassium intoxication, potassium intake should be curtailed. Hard candy provides a potassium-free, calorie-rich adjunct for such situations. Obviously the above program is a minimal one with respect to diet and is designed only as a temporary measure. With diuresis, the patient's appetite may increase and a soft or regular diet is often tolerated and should be encouraged. There is little reason to restrict protein during this phase (see below), and in view of the fact that some protein deficits have been incurred during the acute phase, there

is good reason to encourage full protein intake. One of the reasons that protein is sometimes restricted in patients in this phase is that the level of urea nitrogen may actually increase when full protein intake is allowed. This has been interpreted as indicating that the disease is not healing but rather is passing into a chronic stage. However, this is not the only interpretation of this sequence. In most instances, it is merely a manifestation that GFR does not promptly return to normal, and in the face of a sudden increase in urea formation as a result of full protein intake, urea must rise. Later, with full recovery of function, urea levels fall even though the same level of protein intake has been maintained.

## CHRONIC RENAL FAILURE

Chronic renal failure may be defined as a progressive diffuse diminution of renal tissue generally terminating in uremia. Although a wide variety of conditions may be responsible for such a picture, three are outstanding: chronic glomerulonephritis, chronic pyelonephritis and nephrosclerosis. Although early in the course there are some clinical and pathological differences depending upon the particular etiology, the later stages of these diseases are similar enough to each other to merit consideration together. In fact, pathologically and physiologically the "end-stage kidney" is so diffusely diseased as to defy accurate etiological diagnosis. The rate of development of renal impairment is quite variable; in some patients there is rapid deterioration of function, while in others there may be long periods of quiescence.

Clinically, there may be surprisingly few symptoms pointing toward failure of renal function until terminal uremia occurs. Hypertension, anemia, proteinuria, vascular changes in the retina and a modest degree of polyuria are frequently present, but more often than not it is their accidental discovery which leads to the correct diagnosis. A nephrotic syndrome may punctuate the course of chronic renal failure. This will be discussed separately below.

The clinical picture of terminal uremia consists of a large number of overt disturbances affecting many organs and systems: headache, visual disturbances, weakness, coma, muscular twitching (neuromuscular system); nausea, vomiting, diarrhea, stomatitis (gastrointestinal system); anemia, hemorrhages (hematopoetic system); hypertension, edema and cardiac failure (cardiovascular system) as well as such findings as Kussmaul respiration and uremic "frost," which are the direct effects of metabolic disturbances.

### *Pathophysiology (12)*

The abnormalities or renal function occurring in chronic renal failure affect practically every function the kidney normally performs. Although these abnormalities have usually been attributed to disturbances of the various intrinsic mechanisms as the result of disease, it is likely that many, perhaps all, of the observed abnormalities of chronic renal failure can be attributed to a reduction

in renal mass *per se*. If there is any generalization to the wide range of abnormalities of function in chronic renal failure, it is that the kidney has lost its ability to compensate for these abnormalities due to a marked narrowing of the limits of renal flexibility.

*Glomerular Filtration:* The rate of glomerular filtration is invariably reduced. Although during quiescent stages the level of GFR may be relatively stationary, the inexorable tendency is for progressive diminution until in the terminal stages, filtration virtually ceases. The reduction in GFR has a number of consequences of which elevation of the non-protein nitrogen (NPN) fraction of the blood (azotemia) is the most obvious. This elevation of urea accounts for the greatest part of the rise in NPN in renal disease. Other components of NPN such as uric acid and creatinine also increase, but quantitatively these are small compared to urea (13).

The relationship between the degree of reduction of GFR and the elevation of urea in the plasma is not a simple linear one (14). Hence, significant reductions in GFR may be associated with levels of blood urea which appear to be within the normal range. This type of observation has led to the fallacious concept of "renal reserve," whereby it is thought that very appreciable reductions of renal mass occur before any elevation of blood urea occurs. If nitrogen metabolism remains constant (see above for the importance of this factor in determining the level of urea), then any reduction in GFR will be accompanied by some rise of blood urea. However, since the usually accepted normal values for blood urea are relatively wide, it is possible to have a two-fold increase in urea without exceeding the upper limit of normal. Yet, if this were to occur in any given patient with a constant nitrogen metabolism, it would be a definite abnormality even though the level of urea did not exceed the normal range.

Although the recognition of elevated urea values in the blood historically led to the term uremia, it is now widely recognized that urea *per se* is not the cause of any of the toxic manifestations of renal failure (13). (In fact, no known compound can be incriminated as the cause of uremic symptoms). Elevation of blood urea is physiologically an advantage in that it allows the patient to excrete the urea formed in spite of reduction in GFR.

*Polyuria and Hyposthenuria:* One of the prominent manifestations as the renal lesion progresses is an increase in the daily urinary volume. This often precedes other symptoms and persists until the terminal state when oliguria supervenes. The polyuria is only of moderate proportions in the usual case, but in rare patients very large volumes of urine may be passed, a condition termed "water-losing nephritis" (15).

Accompanying the polyuria is the appearance of a defect in the concentrating power which becomes progressively more severe until a urine of fixed specific gravity is formed (hyposthenuria). Under these latter circumstances the urine is nearly isotonic with the plasma. Not only is there a defect in concentrating

the urine, there is also an inability to undergo a brisk water diuresis with water loading. This latter defect is probably principally related to the reduction in GFR.

One of the most satisfactory explanations for the appearance of polyuria and hyposthenuria in chronic renal failure holds that each nephron still functioning is, in effect, undergoing a solute diuresis (16), the loading solute being urea. As discussed above, the consequence of a solute diuresis is an increase in urinary volume as urinary concentration approaches isotonicity. According to this explanation, there need be no specific intrinsic disturbance of tubular reabsorption of water, but rather a reduction in total number of functioning nephrons in relation to the solute load being presented to the kidneys. In this connection, it is important to note that polyuria and hyposthenuria can be produced in normal rats by the removal of about 75% of the total renal mass (17).

In contrast, "water-losing nephritis" is characterized by much larger urinary volumes; furthermore, in spite of exogenous ADH the urine is consistently hypotonic. For these reasons a specific defect in water reabsorption is most likely.

*Electrolyte Metabolism:* One of the advantages of the "nephron solute diuresis" concept is that it also accounts for the urinary losses of sodium and chloride which are so consistently a part of the metabolic picture of chronic renal failure. The magnitude of these losses in the usual patient ranges from 30 to 60 mEq/L of urine. Although these are not large losses, they are obligatory ones in that when sodium chloride in the diet is restricted these losses continue unabated. This feature of the disease will be discussed more fully below in relation to dietary therapy. Rare patients show much larger losses of sodium ("salt-losing nephritis") which may amount to several hundred mEq per day (18). Because of the severe and rapid salt depletion, patients with "salt-losing nephritis" may present a picture similar to acute adrenal cortical insufficiency. A specific reabsorptive defect involving sodium and chloride is most probably involved.

With respect to potassium, a reduction of renal mass due to disease may be expected to be accompanied by a diminished ability to excrete potassium. Indeed, elevation of serum potassium is common in renal failure, particularly in the advanced stages of the disease (19). It should be remembered, however, that such patients are not immune to the development of potassium deficiency; in fact, because of excessive gastrointestinal losses coupled with a poor intake, potassium depletion is not uncommon, particularly in patients with less than terminal stages of the disease.

*Acidosis:* As chronic renal failure progresses, it is nearly always accompanied by a gradually increasing degree of metabolic acidosis. The latter is reflected chemically in a reduction in serum bicarbonate and in blood pH. Clinically, the acidosis may not be evident until it is severe enough to cause Kussmaul breathing; such overbreathing represents an attempt on the part of the body to ameliorate the acid shift in blood pH through a reduction in $CO_2$ tension and hence in carbonic acid concentration in the plasma.

It has long been recognized that patients with chronic renal failure are unable to respond to an acid load by increasing the rate of excretion of hydrogen ions into the urine (20) as titratable acid or ammonium ion. In the face of an acid load in the form of phosphate and sulfate derived from the diet or from the endogenous metabolism, a metabolic acidosis is produced which the kidneys are unable to correct. Besides phosphate and sulfate there are probably other acids which contribute to the acidosis (see 12). Their nature is not known. Their presence is indicated by the increase in undetermined anions in the plasma which is regularly a feature of advanced renal failure. Finally, because of vomiting and anorexia, uremic patients are perhaps more susceptible than others to the development of starvation ketosis, and such an occurrence may further contribute to the acidosis.

*Abnormalities in calcium and phosphorus metabolism* (21): Significant retention of non-protein nitrogen is nearly always accompanied by some increase in the levels of serum inorganic phosphorus; in far advanced disease, levels three to five times the normal are frequently found. Hypocalcemia occurs apparently secondary to the hyperphosphatemia, but this association is not always found. In response to these abnormalities, the parathyroid glands undergo a hyperplasia. One of the effects of this secondary hyperparathyroidism is to reduce the reabsorption of phosphorus by the proximal tubule. In fact, in far-advanced disease virtually all of the phosphate which is filtered at the glomerulus is excreted. If secondary hyperparathyroidism did not develop, the levels of serum inorganic phosphorus would undoubtedly be even higher.

In spite of hyperphosphatemia and hypocalcemia, overt tetany is uncommon in chronic renal failure apparently because of the protective effect of the concomitant acidosis. However, a positive Chvostek sign indicative of latent tetany is frequent.

The fundamental nature of the metabolic bone disease which accompanies renal failure is incompletely known. The relationship of this type of bone disease ("renal rickets") to other types of rickets is particularly obscure.

Long standing acidosis is certainly of importance in the development of the bone lesions; the direct effect on bone of excessive parathyroid hormone accompanying secondary hyperparathyroidism may contribute to the picture. The operation of still other unknown factors is suggested by the observation that uremic serum inhibits calcification of cartilage.

### *Nutritional Considerations*

In this section, the dietary management of patients with uncomplicated chronic renal failure will be discussed. The therapy of patients during terminal uremia is similar to that outlined for the treatment of the oliguric phase of acute renal failure, which is presented in Part II of this review.

*Water and electrolytes:* The polyuria accompanying chronic renal failure represents an obligatory loss of water from the body which must be replaced. Ordinarily, the patient's own thirst mechanism accurately dictates the need for water intake. Forcing of large water loads orally in an attempt to improve the excretory functions of the diseased kidney does little good and makes the patient uncomfortable. Conditions which limit the oral intake of water demand prompt parenteral provision of water needs.

Losses of sodium in the urine, like those of water, are obligatory in chronic renal failure and must also be promptly replaced. Often because of hypertension or edema, sodium intake is severely restricted. Because of the continuing urinary losses, serious degrees of salt depletion and dehydration may result. This must be avoided since such episodes of salt depletion often provoke further deterioration of residual renal function. The actual level of sodium intake desirable for the patient with chronic renal failure depends upon the circumstances. In patients without significant edema or hypertension, there is no need to restrict sodium. However, except in the early phases of the disease, one or the other of these complications is usually present. The problem can often be solved by measurement of the 24 hour sodium excretion after several days on a given intake of sodium, the attempt being to titrate the patient's intake to a point which approximately equals output so that balance remains close to zero.

*Metabolic Acidosis and Bone Disease:* The decision as to whether the metabolic acidosis accompanying renal failure should be treated must take account of several factors. The acidosis has some protective value against the development of overt hypocalcemic tetany. On the other hand, longstanding severe acidosis has deleterious effects upon bone and is certainly one important factor in the development of the metabolic bone disease accompanying chronic renal failure.

Certainly mild degrees of acidosis which are asymptomatic need not be treated. However, more severe acidosis, particularly if accompanied by clinical, radiological or chemical (elevation of alkaline phosphatase in the serum) evidence of bone disease, should be treated. The preferred salt for treating acidosis of this type by the oral route is sodium citrate to which citric acid usually added (see discussion of renal tubular acidosis below.) Adequacy of therapy should be judged by serial study of the plasma total $CO_2$ content. The attempt should be to raise the total $CO_2$ to 20 to 23 mM/L rather than to frankly normal values, in order to minimize the development of tetany.

Treatment of the acidosis is primary in treatment of bone disease (21). Supplemental calcium (5 gm of Calcium gluconate three times daily) and vitamin D (50,000 I.U./d) constitute additional important measures to insure a positive calcium balance and to raise the serum calcium. Treatment with aluminum hydroxide has also been suggested as a means of reducing the hyperphosphatemia, since this agent binds dietary phosphorus, making it unavailable for absorption. If large doses of this agent are given, serum phosphorus will indeed fall, and serum calcium tends to rise. However, because of the increase in fecal

phosphorus the net phosphorus balance may become negative and bone disease actually will worsen rather than heal.

*Protein and Caloric Intake:* There is no unanimity of opinion on the proper level of protein in the diet of the patient with chronic renal failure. Therefore, it is desirable to present the contrasting points of view.

Proponents of the low protein diet (22) draw their principal arguments from results obtained in experimental animals. For example, rats deprived of three quarters of their renal substance and fed a high protein diet die much quicker than do similarly treated animals receiving a restricted protein intake. Normal rats fed diets extremely high in protein for long periods develop interstitial fibrosis of the kidney as well as glomerular lesions (23).

Another point advanced in favor of protein restriction rests upon the concept that a diminished excretion of urea will reduce the amount of "renal work" and that by analogy with diseases of other organs (*e.g.*, the heart) any reduction in work is desirable. Finally, the argument is advanced that the toxic symptoms of uremia are caused by some as yet unidentified nitrogenous substance derived from the intake of protein accumulating in the serum.

Opponents of the low-protein diet have not let these points go unchallenged. They point out that the studies in experimental animals bear little relevance to the clinical situation since the amounts of protein fed in the experiments far exceed those that would ever be fed to any patient even on a protein-rich diet. Furthermore, in two large carefully studied series of patients recovering from acute glomerulonephritis, high protein diets were not associated with any discernible delay in healing or by any increased incidence in the development of chronic renal failure (24, 25).

The concept of renal work has also been attacked — *e.g.*, measurements of oxygen consumption of the kidney (indicative of renal work) have revealed no changes occurring during a solute diuresis (26). Finally, it should be remembered that there is a large body of experimental evidence demonstrating deleterious effects of protein lack upon renal function and structure in experimental animals (see 13); and these results may have more clinical relevance than those derived from the high protein experiments. Peters and Van Slyke (13) have succinctly summarized their view about the matter as follows: "To condemn (the patient) to invalidism and malnutrition on the doubtful pretext of preserving or prolonging the anatomical and functional integrity of the renal tissue is hardly a defensible policy."

Nonetheless, as implied in the discussion above, there is considerable variation from clinic to clinic with respect to the appropriate level of protein intake for patients with chronic renal failure. In assessing this point for any given patient, the following should receive some consideration: (a) the phase of the disease, (b) the presence or absence of previously incurred protein deficits, (c) the magnitude of the proteinuria, (d) the presence or absence of nausea, vomiting

or diarrhea which limit intake or decrease absorption and (e) the tolerance of the patient to special diets.

Certainly during the early phase of the disease the evidence does not warrant any restriction of protein intake. Too often patients with only slight abnormalities have been placed on severely restricted intakes of protein. This type of ill-advised dietary restriction serves only to substitute protein depletion for asymptomatic renal disease.

In cases of serious deterioration of renal function, most authorities recommend some restriction of protein for one or more of the following reasons: (a) on purely clinical grounds it is claimed the patients feel better, (b) such restriction limits the rise in non-urea nitrogenous compounds in serum and this is desirable in preventing the uremic syndrome, (c) limitation of protein intake is a convenient way of imposing some limitation upon the intake of phosphate, sulfate and potassium, since the latter are frequent accompaniments of protein in foods. Obviously, if protein is too limited, then caloric intake must be made up from carbohydrate and fat. Commercial fat emulsions if tolerated are useful in this connection. A moderate view concerning protein restriction has been expressed by Merrill (27) who advises that patients with serious deterioration of renal function receive 0.5 to 0.7 gm per kilogram of protein of high biological quality.

Greater restriction has been practiced by others (see 28) who advise such diets as the rice diet or a butter-sugar diet.* Force feeding has been particularly stressed by those using the high fat diet.

*A typical high fat of this type is as follows: butter, 100 gm; sugar, 100 gm; rice, 50 gm; flour, 125 gm; fruit, 200 gm; cocoa powder, 10 gm; tea and coffee. This diet provides 2500 Calories, 4 gm. nitrogen, 33 mEq of K, 15 mM of P.

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